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1. Your reference GBP86385

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3 Full name, address and postcode of the or of each applicant (underline all surnames)

Pharma Mar, S.A.,
Calle de la Calera 3
Poligono Industrial de Tres Cantos
Tres Cantos
E-28760 Madrid
Spain

30 JUL 2002

438114100 2

Patents ADP number (if you know it)

If the applicant is a corporate body, give the country/state of its incorporation

Spain

4. Title of the invention TOTAL SYNTHESIS OF MYRIAPORONES

5. Name of your agent (if you have one)
"Address for service" in the United Kingdom to which all correspondence should be sent
(including the postcode)

Marks & Clerk
57 - 60 Lincolns Inn fields
London WC2A 3LS

Patents ADP number (if you know it) 18001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (if you know it) the or each application number

Country	Priority application No (if you know it)	Date of filing (day / month / year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing (day / month / year)

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer 'Yes' if:
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11. I/We request the grant of a patent on the basis of this application.

Signature Nabarro & Clark Date: 30 July 2002

12. Name and daytime telephone number of person to contact in the United Kingdom

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0207 400 3000

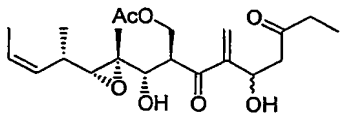
Document : 846394

TOTAL SYNTHESIS OF MYRIAPORONES

The present invention relates to antitumoral compounds and their synthesis, and in particular the total synthesis of miryaporones.

BACKGROUND OF THE INVENTION

Myriaporones are a new class of marine polyketide-derived isolated from the bryozoan *Myriapora truncata*.



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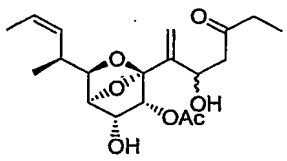

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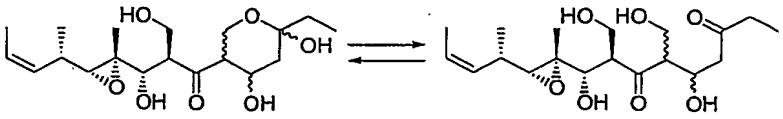
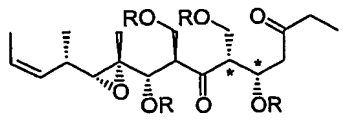


3 4

Miryaporones are disclosed to have antitumor activity. The complete structure for these related compounds was given by K. L. Rinehart et al, *J. Nat. Prod.* **1995**, *58*, 344 and U.S. Patent No. 5,514,708, **1996**. Compound **4** is an equilibrium mixture between the free hydroxy ketone and the hemiketal **3**.

SUMMARY OF THE INVENTION

In a first aspect the present invention is directed to compounds of general formula **5**.



5

wherein the substituent groups defined by R are each independently selected from the group consisting of H, SiR′$_3$, SOR′, SO_2R′, C(=O)R′, C(=O)OR′, C(=O)NR′, substituted or unsubstituted: C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, aryl, heteroaryl or aralkyl;

wherein each of the R′ groups is independently selected from the group consisting of H, OH, NH_2, halogen, substituted or unsubstituted: C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, aryl, heteroaryl or aralkyl;

wherein each of the R groups may be joined into a carbocyclic or heterocyclic system;

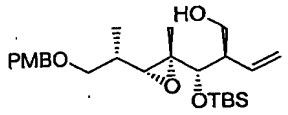
wherein the chiral centers marked with * has the R or the S configuration.

In another aspect the present invention is directed to the synthesis of the compounds of formula 5 as defined above, and to the intermediates used in such a synthetic process.

Another embodiment of the present invention is a pharmaceutical composition comprising the compounds of formula **5** or an intermediate of their synthesis and a pharmaceutically acceptable carrier.

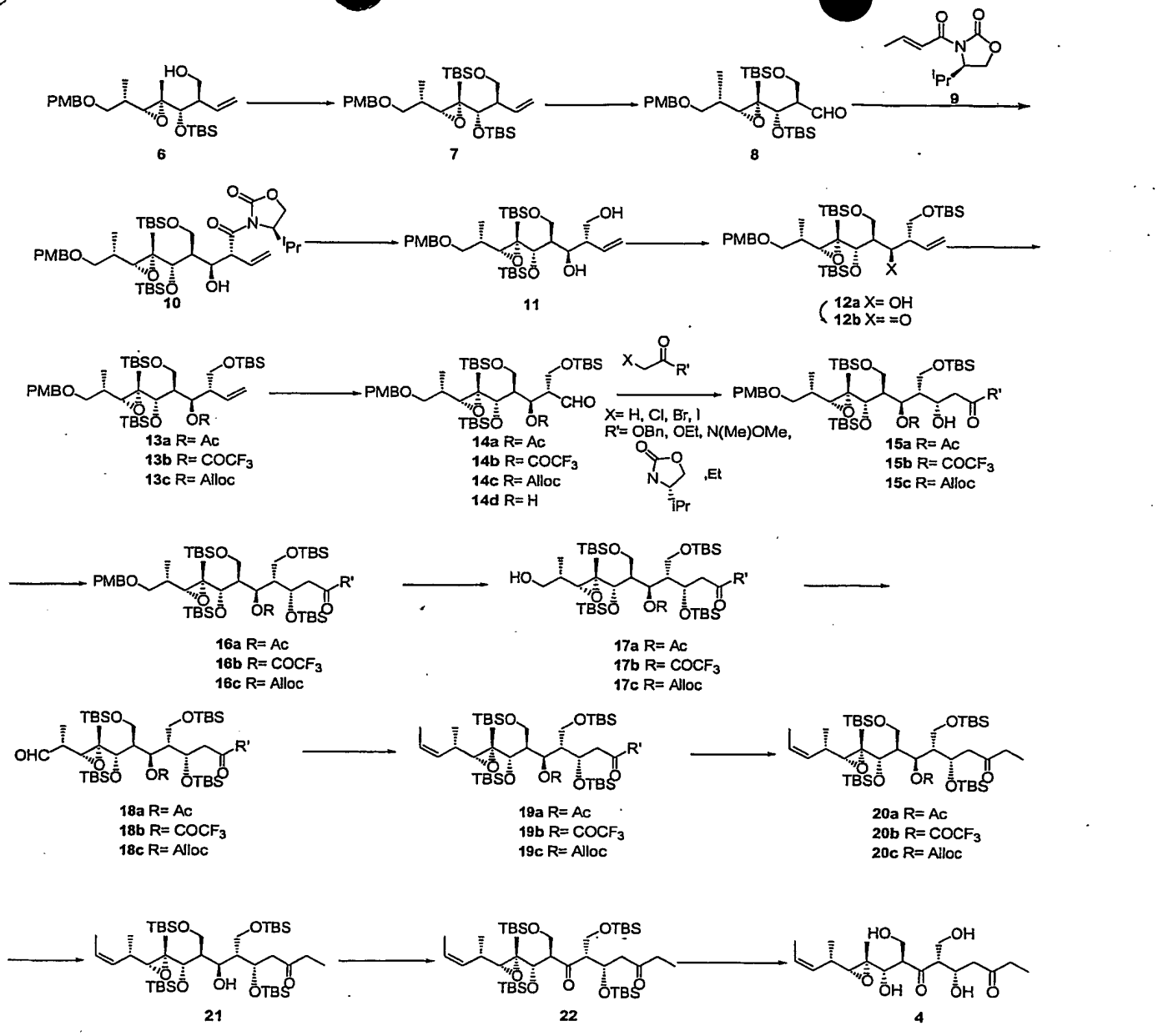
Another embodiment of the present invention is the use of compounds of formula **5** as antitumor agents.

The compounds of the present invention can be synthetically prepared from the intermediate compound **6** described by W. R. Roush et al., *Org. Lett.* **1999**, *1*, 95.



6

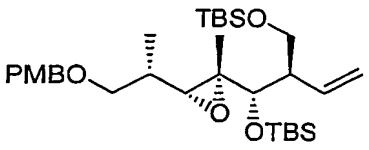
The method of producing compounds of formula **5** is showed in the next Scheme.



The present invention will be further explained with the following examples:

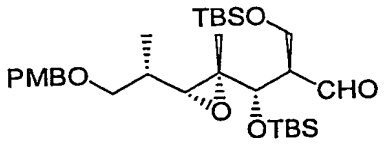
EXPERIMENTAL PART

Example 1: Compound 7



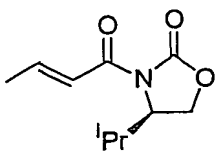
To a solution of **6** (3.51 g, 7.8 mmol) in CH_2Cl_2 (40 mL) was added imidazole (1.59 g, 23.4 mmol) and TBSCl (1.76 g, 11.7 mmol) at 23 °C. The reaction mixture was stirred at 23 °C for 3 h. HCl 0.1 N was added until pH= 4-5, and the mixture was extracted with CH_2Cl_2 (2x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (Hex:EtOAc, 10:1) to obtain compound **7** (3.44 g, 78%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, *J*= 8.7 Hz, 2H), 6.86 (d, *J*= 8.7 Hz, 2H), 5.83 (m, 1H), 4.99 (dd, *J*= 10.5, 1.8 Hz, 1H), 4.86 (dd, *J*= 17.4, 2.1 Hz, 1H), 4.42 (s, 2H), 3.80 (s, 3H), 3.44 (m, 2H), 3.33 (d, *J*= 6.6 Hz, 1H), 2.47 (d, *J*= 9.6 Hz, 1H), 2.24 (m, 1H), 1.75 (m, 1H), 1.08 (d, *J*= 6.6 Hz, 3H), 0.91 (s, 9H), 0.88 (s, 9H), 0.13 (s, 3H), 0.04 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 136.2, 130.3, 129.1, 117.1, 113.7, 72.9, 72.6, 64.9, 64.6, 63.9, 55.2, 51.3, 33.1, 25.9, 25.8, 18.2, 18.1, 14.9, 13.3, -4.2, -5.3, -5.4, -5.5. MS (ESI) m/z: 587 $(M+23)^+$. $[\alpha]^{25}_D$ -9.5 (*c* 0.52, CH_2Cl_2).

Example 2: Compound **8**



To a solution of **7** (0.86 g, 1.52 mmol) in THF:H_2O (10:1, 22 mL) was added NMO (0.623 g, 5.32 mmol) and OsO_4 (4.56 mL, 0.456 mmol, 0.1 M in ^{t}BuOH) at 23 °C and the reaction mixture was stirred at 23 °C overnight. Florisil (6 g), $NaHSO_3$ (6 g), and EtOAc (100 mL) were added and the mixture was stirred vigorously during 30 min. The mixture was filtered through a pad of Celite, and the filtrate was concentrated to provide the corresponding diol. To a solution of this diol in THF (10 mL) was added a solution of $NaIO_4$ (1.95 g, 9.12 mmol) in H_2O (8 mL) at 0 °C and the mixture was stirred at 23 °C for 1 h. The reaction was quenched by addition of a saturated aqueous solution of NH_4Cl (20 mL) and then, extracted with CH_2Cl_2 (2x20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (Hex:EtOAc, 10:1) to afford compound **8** (0.67 g, 78%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.67 (d, *J*= 3.0 Hz, 1H), 7.20 (d, *J*= 8.4 Hz, 2H), 6.84 (d, *J*= 8.4 Hz, 2H), 4.38 (m, 2H), 3.84 (dd, *J*= 10.2, 5.1 Hz, 1H), 3.80 (s, 3H), 3.69 (m, 2H), 3.41 (dd, *J*= 9.3, 5.1 Hz, 1H), 3.31 (t, *J*= 9.0 Hz, 1H), 2.59 (d, *J*= 9.3 Hz, 1H), 2.50 (m, 1H), 1.81 (m, 1H), 1.30 (s, 3H), 1.06 (d, *J*= 6.3 Hz, 3H), 0.86 (s, 18H), 0.14 (s, 3H), 0.04 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.8, 159.5, 130.3, 129.4, 114.0, 76.5, 73.2, 73.0, 65.1, 64.0, 60.1, 57.9, 55.4, 33.6, 26.0, 26.0, 18.3, 15.0, 13.0, -4.0, -5.2, -5.3, -5.5. MS (ESI) m/z: 589 $(M+23)^+$. $[\alpha]^{25}_D$ -11.6 (*c* 0.50, CH_2Cl_2).

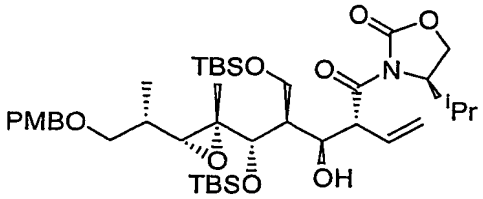
Example 3: Compound **9**



Compound **9** was prepared following the procedure described by D. A. Evans et al. *J. Am. Chem. Soc.* **1984**, *106*, 4261-4263. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (m, 1H), 7.12 (m, 1H),

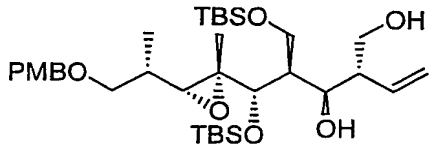
4.44 (m, 1H), 4.20 (m, 2H), 2.36 (m, 1H), 1.91 (dd, *J*= 6.6, 1.2 Hz, 3H), [illegible] (d, *J*= 6.9 Hz, 3H), 0.83 (d, *J*= 6.9 Hz, 3H).

Example 4: Compound **10**



To a solution of **9** (11.2 g, 56.8 mmol) in CH_2Cl_2 (150 mL) was added Bu_2BOTf (62.5 mL, 62.4 mmol) and Et_3N (11.1 mL, 79.5 mmol) at -78 °C. The reaction mixture was stirred 1 h at -78 °C, 15 min at 0 °C and recooled at -78 °C. A solution of **8** (10.7 g, 18.9 mmol) in CH_2Cl_2 (50 mL) was cooled to 0 °C. 50 mL of the solution of **9** was added over the solution of **8** at 0 °C and the reaction mixture was stirred 1 h at 0 °C. The addition was repeated twice in the following 2 hours. Then saturated aqueous solution of NH_4Cl (100 mL) was added and the reaction was extracted with CH_2Cl_2 (2x 120 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (Hex:EtOAc, from 10:1 to 2:1) to afford compound **10** (10.1 g, 70%) as a colourless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.19 (d, *J*= 8.4 Hz, 2H), 6.85 (d, *J*= 8.4 Hz, 2H), 5.93 (m, 1H), 5.41 (d, *J*= 17.1 Hz, 1H), 5.28 (d, *J*= 9.3 Hz, 1H), 4.92 (t, *J*= 9.6 Hz, 1H), 4.63 (dddd, *J*= 9.3, 6.3, 5.1, 1.5 Hz, 1H), 4.43 (s, 3H), 4.34 (m, 1H), 4.12 (m, 2H), 3.85 (m, 1H), 3.80 (s, 3H), 3.73 (m, 2H), 4.44 (m, 2H), 2.58 (d, *J*= 9.3 Hz, 1H), 2.30 (m, 1H), 1.81 (m, 1H), 1.38 (s, 3H), 1.10 (d, *J*= 6.6 Hz, 3H), 0.93 (s, 9H), 0.87 (s, 9H), 0.84 (d, *J*= 7.5 Hz, 3H), 0.80 (d, *J*= 6.9 Hz, 3H), 0.17 (s, 3H), 0.12 (s, 3H), 0.09 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 159.0, 153.3, 135.3, 129.9, 128.6, 113.7, 77.4, 72.6, 71.0, 64.0, 63.4, 62.6, 59.8, 58.4, 58.0, 55.2, 51.2, 45.2, 40.1, 33.6, 26.7, 28.3, 27.8, 26.1, 25.8, 18.3, 17.9, 15.1, 14.6, 14.3, 13.1, -4.4, -5.4, -5.5, -5.6. MS (ESI) m/z: 786 $(M+23)^+$. $[\alpha]^{25}_D$ +3.1 (*c* 0.53, CH_2Cl_2).

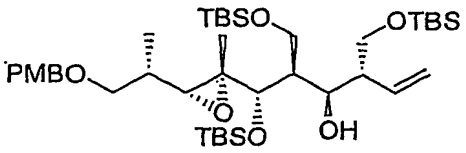
Example 5: Compound **11**



To a solution of **10** (14.5 g, 18.9 mmol) in THF:H_2O (5:1, 120 mL), $LiBH_4$ (94.6 mL, 189.2 mmol, 2.0 M in THF) was added at 0 °C. The reaction mixture was stirred 1 h at 0 °C and 2 h at 23 °C. Saturated aqueous solution of NH_4Cl (100 mL) was added and the mixture was extracted with EtOAc (3x100 mL). The combined organic layers were washed with NaOH 1 N (2x100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (Hex:EtOAc, 10:1) to afford **11** (7.99 g, 66%) as a colourless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.22 (d, *J*= 8.4 Hz, 2H), 6.87 (d, *J*= 8.4 Hz, 2H), 5.84 (m, 1H), 5.21 (d, *J*= 8.7 Hz, 1H), 5.14 (d, *J*= 17.4 Hz, 1H), 4.42 (s, 2H), 4.19 (m, 1H), 3.84 (m, 1H), 3.80 (s, 3H), 3.75 (m, 1H), 3.61 (m, 2H), 3.48 (m, 2H), 3.36 (m, 2H), 2.53 (d, *J*= 9.3 Hz, 1H), 2.27 (m, 1H), 1.80 (m, 1H), 1.32 (s, 3H), 1.05 (d, *J*= 6.9 Hz, 3H), 0.91 (s, 9H), 0.88 (s, 9H), 0.15 (s, 3H), 0.09 (s, 3H), 0.05 (s, 3H), 0.04 (s,

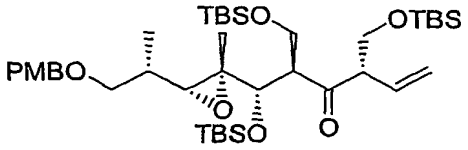
3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 137.6, 130.3, 129.4, 118.3, 114.0, 73.2, 73.0, 71.2, 64.9, 64.4, 60.4, 55.5, 51.1, 47.0, 33.5, 29.9, 26.4, 26.3, 26.0, 18.4, 18.2, 15.0, 14.0, -4.2, -5.1, -5.2. MS (ESI) m/z: 662 $(M+23)^+$.

Example 6: Compound **12a**



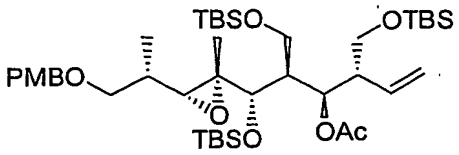
To a solution of **11** (7.43 g, 11.6 mmol) in CH_2Cl_2 (100 mL) was added imidazole (3.16 g, 46.4 mmol) and TBSCl (3.48 g, 23.2 mmol) at 23 °C. The reaction mixture was stirred at 23 °C for 12 h. 0.1N HCl was added until pH= 4-5, and the reaction was extracted with CH_2Cl_2 (2x150 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (Hex:EtOAc, from 10:1 to 4:1) to obtain compound **12a** (8.47 g, 97%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (d, *J*= 8.6 Hz, 2H), 6.86 (d, *J*= 8.6 Hz, 2H), 5.86 (m, 1H), 5.07 (m, 2H), 4.41 (m, 2H), 4.29 (br s, 1H), 3.88 (m, 1H), 3.80 (s, 3H), 3.74 (m, 1H), 3.62 (m, 2H), 3.48 (m, 1H), 3.34 (d, *J*= 6.8 Hz, 2H), 3.17 (d, *J*= 4.9 Hz, 1H), 2.55 (d, *J*= 9.2 Hz, 1H), 2.26 (m, 1H), 1.78 (m, 2H), 1.32 (s, 3H), 1.06 (d, *J*= 6.6 Hz, 3H), 0.92 (s, 9H), 0.88 (s, 9H), 0.87 (s, 9H), 0.16 (s, 3H), 0.10 (s, 3H), 0.05 (s, 3H), 0.03 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 138.0, 130.5, 129.2, 117.1, 114.0, 77.4, 73.1, 72.8, 69.4, 65.0, 64.8, 64.5, 60.7, 55.4, 51.9, 46.9, 33.7, 29.9, 26.3, 26.2, 26.1, 18.6, 18.5, 18.1, 15.1, 13.5, -4.3, -5.0, -5.1, -5.2. MS (ESI) m/z: 775 $(M+23)^+$, 753 $(M+1)^+$.

Example 7: Compound **12b**



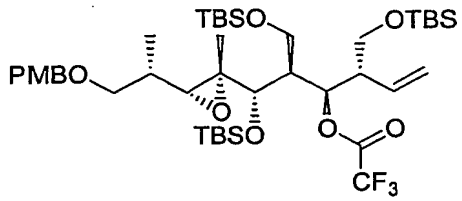
To a solution of **12a** (500 mg, 0.663 mmol) in CH_2Cl_2 (30 mL) was added Dess-Martin periodinane (562 mg, 1.32 mmol) at 23 °C. The reaction mixture was stirred at 23 °C for 3 h. Saturated aqueous solution of $NaHCO_3$ (30 mL) was added and the mixture was extracted with CH_2Cl_2 (3x 40 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (Hex:EtOAc, 10:1) to obtain compound **12b** (414 mg, 83%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, *J*= 8.4 Hz, 2H), 6.87 (d, *J*= 8.4 Hz, 2H), 5.78 (m, 1H), 5.23 (m, 2H), 4.42 (dd, *J*= 16.2, 11.4, 2H), 4.02 (dd, *J*= 10.2, 4.8 Hz, 1H), 3.81 (s, 3H), 3.74 (m, 1H), 3.61 (m, 2H), 3.33 (m, 3H), 2.48 (d, *J*= 9.3 Hz, 1H), 1.77 (m, 1H), 1.29 (s, 3H), 1.06 (d, *J*= 6.6 Hz, 3H), 0.87 (s, 9H), 0.86 (s, 9H), 0.84 (s, 9H), 0.11 (s, 3H), 0.04 (s, 3H), 0.03, (s, 3H), 0.02, (s, 3H), -0.01, (s, 3H), -0.03 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.2, 159.1, 134.3, 130.2, 129.0, 119.3, 113.7, 77.5, 72.7, 72.2, 64.3, 63.0, 62.3, 62.2, 61.1, 55.9, 55.2, 33.6, 29.7, 26.0, 25.9, 25.8, 18.2, 18.1, 15.0, 12.2, -4.5, -5.2, -5.3, -5.4, -5.4, -5.5. MS (ESI) m/z: 773 $(M+23)^+$.

Example 8: Compound **13a**



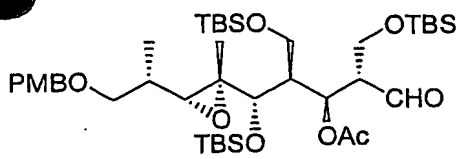
To a solution of **12a** (1.5 g, 1.99 mmol) in THF (30 mL) was added Et_3N (5.55 mL, 39.82 mmol), DMAP (24 mg, 0.119 mmol) and Ac_2O (1.88 mL, 19.91 mmol) at 0 °C. The reaction mixture was stirred at 23 °C for 12 h. Saturated aqueous solution of $NaHCO_3$ (50 mL) was added and the mixture was extracted with CH_2Cl_2 (3x50 mL). The combined organic layers were washed with 0.1N HCl (2x50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (Hex:EtOAc, 10:1) to obtain compound **13a** (1.12 g, 71%) as a colourless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, *J*= 8.5 Hz, 2H), 6.86 (d, *J*= 8.5 Hz, 2H), 5.66 (m, 1H), 5.48 (m, 1H), 5.09 (m, 2H), 4.42 (m, 2H), 3.80 (s, 3H), 3.60 (m, 2H), 3.46 (m, 2H), 3.34 (m, 4H), 2.61 (m, 1H), 2.48 (d, *J*= 9.1 Hz, 1H), 1.95 (s, 3H), 1.77 (m, 1H), 1.34 (s, 3H), 1.06 (d, *J*= 6.6 Hz, 3H), 0.91 (s, 9H), 0.88 (s, 9H), 0.86 (s, 9H), 0.11 (s, 3H), 0.05 (s, 3H), 0.03 (s, 6H), 0.01 (s, 3H), -0.01 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8, 159.4, 136.7, 130.6, 129.3, 118.3, 114.0, 76.9, 73.0, 72.6, 70.6, 64.4, 59.9, 55.4, 52.5, 47.1, 33.4, 26.3, 26.1, 26.1, 21.4, 18.6, 18.3, 15.2, 13.3, -4.1, -4.9, -5.0, -5.1, -5.2, -5.2. MS (ESI) m/z: 817 $(M+23)^+$, 812 $(M+18)^+$.

Example 9: Compound **13b**



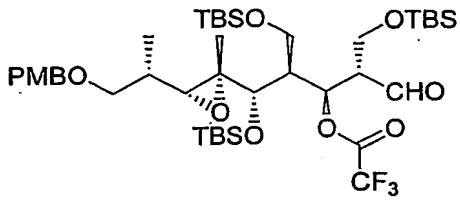
To a solution of **12a** (215 mg, 0.285 mmol) in THF (5 mL) was added Py (0.46 mL, 5.7 mmol), DMAP (53 mg, 0.427 mmol) and $(CF_3CO)_2O$ (0.40 mL, 2.85 mmol) at 0 °C. The reaction mixture was stirred at 23 °C for 12 h. Saturated aqueous solution of $NaHCO_3$ (7 mL) was added and the reaction was extracted with CH_2Cl_2 (3x10 mL). The combined organic layers were washed with HCl 0.1N (2x4 mL),dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (Hex:EtOAc, 18:1) to obtain compound **13b** (221 mg, 91%) as a colourless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.22 (d, *J*= 8.7 Hz, 2H), 6.87 (d, *J*= 8.7 Hz, 2H), 5.75 (m, 1H), 5.65 (m, 1H), 5.09 (m, 2H), 4.42 (s, 2H), 3.81 (s, 3H), 3.47 (m, 8H), 2.78 (m, 1H), 2.51 (d, *J*= 9.0 Hz, 1H), 2.11 (m, 1H), 1.78 (m, 1H), 1.33 (s, 3H), 1.06 (d, *J*= 6.9 Hz, 3H), 0.91 (s, 9H), 0.88 (s, 18H), 0.12 (s, 3H), 0.06 (s, 3H), 0.03 (s, 3H), 0.01 (s, 6H), 0.00 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 156.0 (d, J_{C-F}= 41.0 Hz), 134.6, 130.2, 129.1, 119.4, 113.8, 76.0, 75.4, 72.9, 72.7, 64.3, 64.0, 63.8, 59.3, 55.2, 51.6, 46.2, 33.1, 26.1, 25.9,18.3, 18.0, 14.8, 14.1, 13.2, -4.5, -5.0, -5.4, -5.5, -5.6, -5.7. MS (ESI) m/z: 866 $(M+18)^+$.

Example 10: Compound **14a**



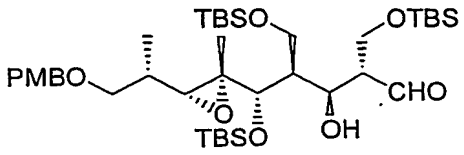
To a solution of **13a** (2.25 g, 2.84 mmol) in THF:H_2O (70:30, 105 mL) was added NMO (1.16 g, 9.94 mmol) and OsO_4 (5.68 mL, 0.568 mmol, 0.1 M in ^tBuOH) at 23 °C and the reaction mixture was stirred at 23 °C overnight. Florisil (16 g), $NaHSO_3$ (16 g), and EtOAc (160 mL) were added and the mixture was stirred vigorously during 30 min. The mixture was filtered through a pad of Celite, and the filtrate was concentrated to provide the corresponding diol. This diol was dissolved in anhydrous Toluene (50 mL) and $Pb(OAc)_4$ (1.57 g, 3.55 mmol) was added at 0 °C, stirred for 30 min, filtered through a pad of Celite, washed with EtOAc and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (Hex:EtOAc, 20:1) to afford compound **14a** (0.97 g, 43%) as a colourless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 9.61 (d, *J*= 3.9 Hz, 1H), 7.22 (d, *J*= 8.5 Hz, 2H), 6.87 (d, *J*= 8.5 Hz, 2H), 5.56 (dd, *J*= 10.3, 6.6 Hz, 1H), 4.42 (s, 2H), 3.95 (m, 1H), 3.80 (s, 3H), 3.54 (m, 2H), 3.38 (d, *J*= 7.0 Hz, 2H), 3.24 (d, *J*= 6.8 Hz, 1H), 3.04 (m, 1H), 2.49 (d, *J*= 9.0 Hz, 1H), 1.98 (s, 3H), 1.79 (m, 1H), 1.31 (s, 3H), 1.06 (d, *J*= 6.8 Hz, 3H), 0.92 (s, 9H), 0.88 (s, 9H), 0.85 (s, 9H), 0.13 (s, 3H), 0.06 (s, 6H), 0.04 (s, 3H), 0.03 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.3, 170.1, 159.4, 130.4, 129.3, 114.0, 76.6, 73.1, 72.7, 69.1, 64.4, 63.9, 61.3, 60.0, 58.4, 55.4, 46.4, 33.4, 29.9, 26.4, 26.1, 26.0, 21.2, 18.6, 18.4, .18.3, 15.1, 12.8, -4.1, -5.0, -5.1, -5.2, -5.3, -5.4. MS (ESI) m/z: 819 $(M+23)^+$.

Example 11: Compound **14b**



To a solution of **13b** (241 mg, 0.285 mmol) in THF:H_2O (70:30, 14 mL) was added NMO (117 mg, 1.0 mmol) and OsO_4 (0.85 mL, 0.085 mmol, 0.1 M in ^tBuOH) at 23 °C and the reaction mixture was stirred at 23 °C overnight. Florisil (1.5 g), $NaHSO_3$ (1.5 g), and EtOAc (30 mL) were added and the mixture was stirred vigorously. After 30 min, this mixture was filtered through a pad of Celite, and the filtrate was concentrated to provide the corresponding diol. This diol was dissolved in anhydrous Toluene (30 mL) and $Pb(OAc)_4$ (158 mg, 0.356 mmol) was added at 0 °C, stirred for 10 min, filtered through a pad of Celite, washed with EtOAc and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (Hex:EtOAc, 19:1) to afford compound **14b** (128 mg, 53%) as a white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 9.80 (d, *J*= 3.0 Hz, 1H), 7.20 (d, *J*= 8.7 Hz, 2H), 6.86 (d, *J*= 8.7 Hz, 2H), 4.66 (m, 1H), 4.40 (s, 2H), 3.86 (m, 2H), 3.80 (s, 3H), 3.69 (m, 2H), 3.62 (m, 2H), 3.36 (m, 2H), 2.59 (d, *J*= 9.3 Hz, 1H), 2.46 (m, 1H), 1.81 (m, 1H), 1.72 (m, 1H), 1.29 (s, 3H), 1.06 (d, *J*= 6.6 Hz, 3H), 0.92 (s, 6H), 0.87 (s, 6H), 0.85 (s, 6H), 0.16 (s, 3H), 0.11 (s, 3H), 0.06 (s, 6H), 0.01 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.4, 159.2, 130.0, 129.1, 113.7, 76.4, 72.9, 72.7, 68.0, 64.6, 63.9, 60.8, 60.1, 57.7, 55.2, 44.4, 33.5, 29.7, 26.1, 25.7, 18.3, 18.1, 17.8, 14.8, 12.9, -4.6, -5.3, -5.5, -5.5, -5.7, -5.7.

Example 12: Compound **14d**



To a solution of **12a** (500 mg, 0.663 mmol) in THF:H_2O (70:30, 28 mL) was added NMO (273 mg, 2.32 mmol) and OsO_4 (1.33 mL, 0.132 mmol, 0.1 M in ^tBuOH) at 23 °C and the reaction mixture was stirred at 23 °C overnight. Florisil (3.5 g), $NaHSO_3$ (3.5 g), and EtOAc (60 mL) were added and the mixture was stirred vigorously. After 30 min, this mixture was filtered through a pad of Celite, and the filtrate was concentrated to provide the corresponding diol. This diol was dissolved in anhydrous Toluene (20 mL) and $Pb(OAc)_4$ (367 mg, 0.828 mmol) was added at 0 °C, stirred for 30 min, filtered through a pad of Celite, washed with EtOAc and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (Hex:EtOAc, 15:1) to afford compound **14d** (228 mg, 46%) as a colourless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 9.80 (d, *J*= 3.0 Hz, 1H), 7.20 (d, *J*= 8.7 Hz, 2H), 6.85 (d, *J*= 8.7 Hz, 2H), 4.66 (m, 1H), .439 (s, 2H), 3.84 (m, 2H), 3.78 (s, 3H), 3.68 (m, 2H), 3.61 (m, 2H), 3.37 (m, 2H), 2.58 (d, *J*= 9.0 Hz, 1H), 2.44 (m, 1H), 1.82 (m, 1H), 1.72 (m, 1H), 1.29 (s, 3H), 1.05 (d, *J*= 6.6 Hz, 3H), 0.91 (s, 9H), 0.87 (s, 9H), 0.85 (s, 9H), 0.15 (s, 3H), 0.11 (s, 3H), 0.06 (s, 6H), 0.00 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.3, 159.2, 130.0, 129.0, 113.7, 76.4, 72.8, 72.7, 67.9, 64.6, 63.9, 60.8, 60.1, 57.7, 55.1, 44.4, 33.5, 26.1, 25.7, 18.3, 18.1, 17.8, 14.8, 12.9, -4.6, -5.3, -5.5, -5.5, -5.7, -5.7.

Alkyl groups preferably have from 1 to 24 carbon atoms. One more preferred class of alkyl groups has 1 to about 12 carbon atoms, yet more preferably 1 to about 8 carbon atoms, still more preferably 1 to about 6 carbon atoms, and most preferably 1, 2, 3 or 4 carbon atoms. Another more preferred class of alkyl groups has 12 to about 24 carbon atoms, yet more preferably 12 to about 18 carbon atoms, and most preferably 13, 15 or 17 carbon atoms. Methyl, ethyl and propyl including isopropyl are particularly preferred alkyl groups in the compounds of the present invention. As used herein, the term alkyl, unless otherwise modified, refers to both cyclic and noncyclic groups, although cyclic groups will comprise at least three carbon ring members.

Preferred alkenyl and alkynyl groups in the compounds of the present invention have one or more unsaturated linkages and from 2 to about 12 carbon atoms, more preferably 2 to about 8 carbon atoms, still more preferably 2 to about 6 carbon atoms, even more preferably 1, 2, 3 or 4

carbon atoms. The terms alkenyl and alkynyl as used herein refer to both cyclic and noncyclic groups, although straight or branched noncyclic groups are generally more preferred.

Preferred alkoxy groups in the compounds of the present invention include groups having one or more oxygen linkages and from 1 to about 12 carbon atoms, more preferably from 1 to about 8 carbon atoms, and still more preferably 1 to about 6 carbon atoms, and most preferably 1, 2, 3 or 4 carbon atoms.

Preferred alkylsulfinyl groups in the compounds of the present invention include those groups having one or more sulfoxide (SO) groups and from 1 to about 12 carbon atoms, more preferably from 1 to about 8 carbon atoms, and still more preferebly 1 to about 6 carbon atoms. Alkylsulfinyl groups having 1, 2, 3 or 4 carbon atoms are particularly preferred.

Preferred alkylsulfonyl groups in the compounds of the present invention include those groups having one or more sulfonyl (SO_2) groups and from 1 to about 12 carbon atoms, more preferably from 1 to about 8 carbon atoms, and still more preferably 1 to about 6 carbon atoms. Alkylsulfonyl groups having 1, 2, 3 or 4 carbon atoms are particularly preferred.

Preferred aminoalkyl groups include those groups having one or more primary, secondary and/or tertiary amine groups, and from 1 to about 12 carbon atoms, more preferably 1 to about 8 carbon atoms, still more preferably 1 to about 6 carbon atoms, even more preferably 1, 2, 3 or 4 carbon atoms. Secondary and tertiary amine groups are generally more preferred than primary amine moieties.

Suitable heterocyclic groups include heteroaromatic and heteroalicyclic groups. Suitable heteroaromatic groups in the compounds of the present invention contain one, two or three heteroatoms selected from N,

O or S atoms and include, e.g., coumarinyl including 8-coumarinyl, quinolinyl including 8-quinolinyl, pyridyl, pyrazinyl, pyrimidyl, furyl, pyrrolyl, thienyl, thiazolyl, oxazolyl, imidazolyl, indolyl, benzofuranyl and benzothiazol. Suitable heteroalicyclic groups in the compounds of the present invention contain one, two or three heteroatoms selected from N, O or S atoms and include, e.g., tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, morpholino and pyrrolindinyl groups.

Suitable carbocyclic aryl groups in the compounds of the present invention include single and multiple ring compounds, including multiple ring compounds that contain separate and/or fused aryl groups. Typical carbocyclic aryl groups contain 1 to 3 separate or fused rings and from 6 to about 18 carbon ring atoms. Specifically preferred carbocyclic aryl groups include phenyl including substituted phenyl such as 2-substituted phenyl, 3-substituted phenyl, 2.3-substituted phenyl, 2.5-substituted phenyl, 2.3.5-substituted and 2.4.5-substituted phenyl, including where one or more of the phenyl substituents is an electron-withdrawing group such as halogen, cyano, nitro, alkanoyl, sulfinyl, sulfonyl and the like; naphthyl including 1-naphthyl and 2-naphthyl; biphenyl; phenanthryl; and anthracyl.

References herein to substituted groups in the compounds of the present invention refer to the specified moiety, typically alkyl or alkenyl, that may be substituted at one or more available positions by one or more suitable groups, e.g., halogen such as fluoro, chloro, bromo and iodo; cyano; hydroxyl; nitro; azido; alkanoyl such as a C1-6 alkanoyl group such as acyl and the like; carboxamido; alkyl groups including those groups having 1 to about 12 carbon atoms or from 1 to about 6 carbon atoms and more preferably 1-3 carbon atoms; alkenyl and alkynyl groups including groups having one or more unsaturated linkages and from 2 to about 12 carbon or from 2 to about 6 carbon atoms; alkoxy groups having those having one or more oxygen linkages and from 1 to about 12 carbon atoms or 1 to about 6 carbon atoms; aryloxy such as phenoxy; alkylthio groups including those moieties having one or more thioether linkages and from 1 to about 12

carbon atoms or from 1 to about 6 carbon atoms; alkylsulfinyl groups including those moieties having one or more sulfinyl linkages and from 1 to about 12 carbon atoms or from 1 to about 6 carbon atoms; alkylsulfonyl groups including those moieties having one or more sulfonyl linkages and from 1 to about 12 carbon atoms or from 1 to about 6 carbon atoms; aminoalkyl groups such as groups having one or more N atoms and from 1 to about 12 carbon atoms or from 1 to about 6 carbon atoms; carbocylic aryl having 6 or more carbons, particularly phenyl (e.g., R being a substituted or unsubstituted biphenyl moiety); and aralkyl such as benzyl; heterocyclic groups including heteroalicyclic and heteroaromatic groups, especially with 5 to 10 ring atoms of which 1 to 4 are heteroatoms, more preferably heterocyclic groups with 5 or 6 ring atoms and 1 or 2 heteratoms or with 10 ring atoms and 1 to 3 heteroatoms.

Preferred R' groups are present in groups of formula R', COR' or OCOR' and include alkyl or alkenyl, that may be substituted at one or more available positions by one or more suitable groups, e.g., halogen such as fluoro, chloro, bromo and iodo, especially ω-chloro or perfluoro; aminoalkyl groups such as groups having one or more N atoms and from 1 to about 12 carbon atoms or from 1 to about 6 carbon atoms; carbocylic aryl having 6 or more carbons, particularly phenyl; and aralkyl such as benzyl; heterocyclic groups including heteroalicyclic and heteroaromatic groups, especially with 5 to 10 ring atoms of which 1 to 4 are heteroatoms, more preferably heterocyclic groups with 5 or 6 ring atoms and 1 or 2 heteratoms or with 10 ring atoms and 1 to 3 heteroatoms, the heterocyclic groups optionally being substituted with one or more of the subsitituents permitted for R' and especially amino such as dimethylamino or with keto.

Suitable halogen substituents in the compounds of the present invention include F, Cl, Br and I.

The invention provides new compounds which differ from the known myriaporones. The new compounds may differ isomerically or otherwise.

The invention also extends to equilibrium isomers of the compounds of formula 5, notably where a hydroxyketone forms a ketal.

In one class of compounds of this invention, the substituent at carbon 17 (see US 5514708 for numbering system) is not OH or OAc. More preferably, the substituent has at least 4, 5 or 6 carbon atoms and/or is not OH or OCOR'.

Another especially preferred embodiment of the present invention is pharmaceutical compositions useful as antitumor agents which contain as active ingredient a compound or compounds of the invention, as well as the processes for their preparation.

Examples of pharmaceutical compositions include any solid (tablets, pills, capsules, granules etc.) or liquid (solutions, suspensions or emulsions) with suitable composition or oral, topical or parenteral administration.

Administration of the compounds or compositions of the present invention may be any suitable method, such as intravenous infusion, oral preparation, intraperitoneal and intravenous preparation. We prefer that infusion times of up to 24 hours are used, more preferably 2-12 hours, with 2-6 hours most preferred. Short infusion times which allow treatment to be carried out without an overnight stay in hospital are especially desirable. However, infusion may be 12 to 24 hours or even longer if required. Infusion may be carried out at suitable intervals of say 2 to 4 weeks. Pharmaceutical compositions containing compounds of the invention may be delivered by liposome or nanosphere encapsulation, in sustained release formulations or by other standard delivery means.

The correct dosage of the compounds will vary according to the particular formulation, the mode of application, and the particular situs, host and tumour being treated. Other factors like age, body weight, sex,

diet, time of administration, rate of excretion, condition of the host, drug combinations, reaction sensitivities and severity of the disease shall be taken into account. Administration can be carried out continuously or periodically within the maximum tolerated dose.

The compounds and compositions of this invention may be used with other drugs to provide a combination therapy. The other drugs may form part of the same composition, or be provided as a separate composition for administration at the same time or a different time. The identity of the other drug is not particularly limited, and suitable candidates include:

a) drugs with antimitotic effects, especially those which target cytoskeletal elements, including microtubule modulators such as taxane drugs (such as taxol, paclitaxel, taxotere, docetaxel), podophylotoxins or vinca alkaloids (vincristine, vinblastine);

b) antimetabolite drugs such as 5-fluorouracil, cytarabine, gemcitabine, purine analogues such as pentostatin, methotrexate);

c) alkylating agents such as nitrogen mustards (such as cyclophosphamide or ifosphamide);

d) drugs which target DNA such as the antracycline drugs adriamycin, doxorubicin, pharmorubicin or epirubicin;

e) drugs which target topoisomerases such as etoposide;

f) hormones and hormone agonists or antagonists such as estrogens, antiestrogens (tamoxifen and related compounds) and androgens, flutamide, leuprorelin, goserelin, cyprotrone or octreotide;

g) drugs which target signal transduction in tumour cells including antibody derivatives such as herceptin;

h) alkylating drugs such as platinum drugs (cis-platin, carbonplatin, oxaliplatin, paraplatin) or nitrosoureas;

i) drugs potentially affecting metastasis of tumours such as matrix metalloproteinase inhibitors;

j) gene therapy and antisense agents;

k) antibody therapeutics;

l) other bioactive compounds of marine origin, notably the didemnins such as aplidine;

m) steroid analogues, in particular dexamethasone;

n) anti-inflammatory drugs, in particular dexamethasone; and

o) anti-emetic drugs, in particular dexamethasone.

In the reaction scheme on page 3, the protecting group TBS and PMB may be replaced by other groups. Examples of hydroxy protecting groups are to be seen, for example, in WO 0069862 at pages 19 and 20. Each of the separate steps in the scheme is a process of this reaction. The groups R shown in the scheme can be varied to other substituents, notably other groups R in the general formula 5 and other hydroxy protecting groups. The group shown as R' in the scheme can also be varied, and be a group R defined in the general formula 5. This terminal substituent can be carried through to the end compounds of this invention, and thus it is not necessary to have an ethyl group at the position alpha to the keto group. Other activating groups in place of the indicated X may be employed. The identity of the compound 9 can be changed to allow for other ways to get from the compound 8 to the compound 11.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